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A REVIEW OF THE ROLE OF MELATONIN LEVELS IN NEOPLASTIC DEVELOPMENT

by

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A brief literature review of the relevant literature was carried out to determine the validity of the hypothesis that melatonin suppression could influence the cancer incidences reported in EMF studies. Evidence was found of melatonin suppression by electric fields, and sensitivity of rodents to magnetic fields. Removal of the melatonin producing organ (pinealectomy) in most animal studies resulted in tumor stimulation, while administration of melatonin in the PM to functionally pinealectomized rodents usually resulted in tumor inhibition. Suggestions were found that melatonin impacts the effectiveness of the immune system. It was concluded that melatonin likely plays a role in neoplastic development although the complete mechanism is unknown.

There has been increasing interest in the suggestion that electromagnetic fields may have deleterious effects on human health. Recent epidemiologic studies have linked exposure to electric and magnetic fields to increased risk for several types of cancer (1,2,3,4). This possible association between fields and cancer has led to the development of several hypotheses that outline possible mechanisms for such effects. If electric and/or magnetic fields affect the aetiology of cancer at all, their effect is likely to be extremely subtle. It has been suggested that electromagnetic fields may act as promoters and there is a lack of sufficient additional evidence to support this hypothesis. Presently, there is no conclusive experimental evidence of any association.

An alternative hypothesis proposes that electric and/or magnetic fields may exert effects via a more indirect mechanism, by influencing the secretion of melatonin by the pineal gland. Experimental evidence demonstrates that melatonin can influence the development and proliferation of cancer (7,8). Additional evidence indicates that fields may suppress melatonin levels (9), and may, in this way affect the progression of cancer. This would result in the acceleration of growth of already established tumors, rather than the development of new cancers. Leung et al (5,6) found increased numbers of tumors per animal in rats induced with DMBA and exposed to electric fields. A brief review of the relevant literature is presented, to determine the validity of this hypothesis.

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The pineal gland is an important neuroendocrine organ, located in the brain (15). It functions as a transducer, translating a large variety of external and internal signals into adaptive neuroendocrine changes that allow the organism to adapt to the environment and coordinate its responses (25). It is part of the mechanism that allows the body and brain to sense changes in environmental factors such as light and temperature and initiate adjustments to internal functions such as sleep, endocrine rhythms and behaviour. The pineal gland and its secretions also play a major role in the regulation and synchronization of seasonal and circadian rhythms. The complete physiology of the human pineal gland has yet to be detailed. In contrast, the role of the pineal gland in animals is more fully established (10).

The most intensively studied pineal hormone is N-acetyl-5-methoxytryptamine, or melatonin. Melatonin is synthesized in the pinealocyte according to the pathway in figure 1 (10).

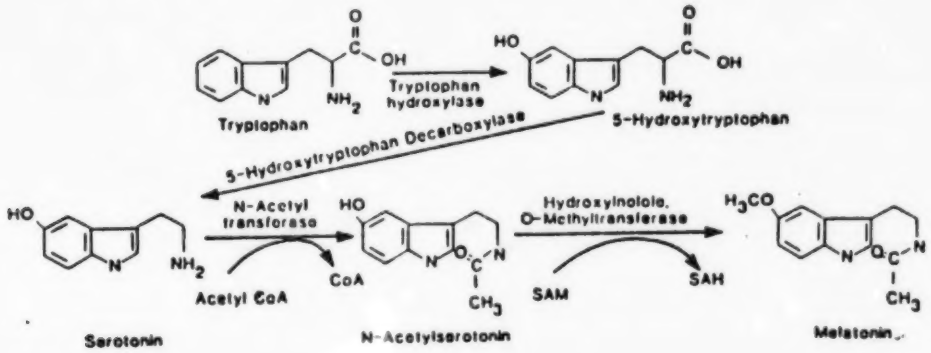

FIGURE 1: THE BIOSYNTHESIS OF MELATONIN (10)

Its synthesis and release is modulated by noradrenergic mechanisms. Noradrenaline released from post ganglionic sympathetic nerves activates pineal β-adrenergic receptors (10,12,16). Melatonin secretion can be pharmacologically inhibited by β receptor antagonists (15,17) and stimulated by noradrenaline uptake inhibitors (11, 12). Binding sites for melatonin have been found in the pineal, eyes, nerves, brain, pituitary and gonads, but whether the hormone has any direct effects at these sites is still under study. Melatonin does exert effects on the endocrine products of the pituitary gland, such as growth hormone, prolactin, lutenizing hormone and follicle stimulating hormone (15). A hypothetical relationship between the pineal and other organs is illustrated in figure 2 (13).

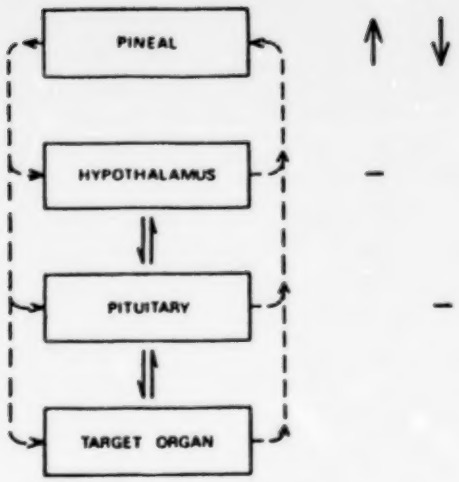

FIGURE 2: SCHEMATIC HYPOTHETICAL RELATIONSHIPS BETWEEN PINEAL, HYPOTHALAMIC, PITUITARY AND TARGET ORGANS (13)

Melatonin is found primarily in serum, but is also present in urine, cerebrospinal fluid and saliva (10). The serum levels of melatonin are very consistent from day to day in the same individual but vary markedly between individuals (10, 12).

The pattern of melatonin levels in humans displays a 24 hour cycle of circadian rhythm with a diurnal variation in output. The daytime levels are very low, rising to a maximum concentration during the night (10,13). No difference in melatonin levels have been found in females vs males, when body size is taken into account (15). Figure 3 illustrates the melatonin profiles of several normal individuals (10). Melatonin levels also vary seasonally (13, 15), with peak values in humans occurring in the winter and summer and lower values in the spring and autumn (17). In some mammals this cyclical change plays a role in the regulation of seasonal breeding patterns (20) and other seasonal rhythms (12).

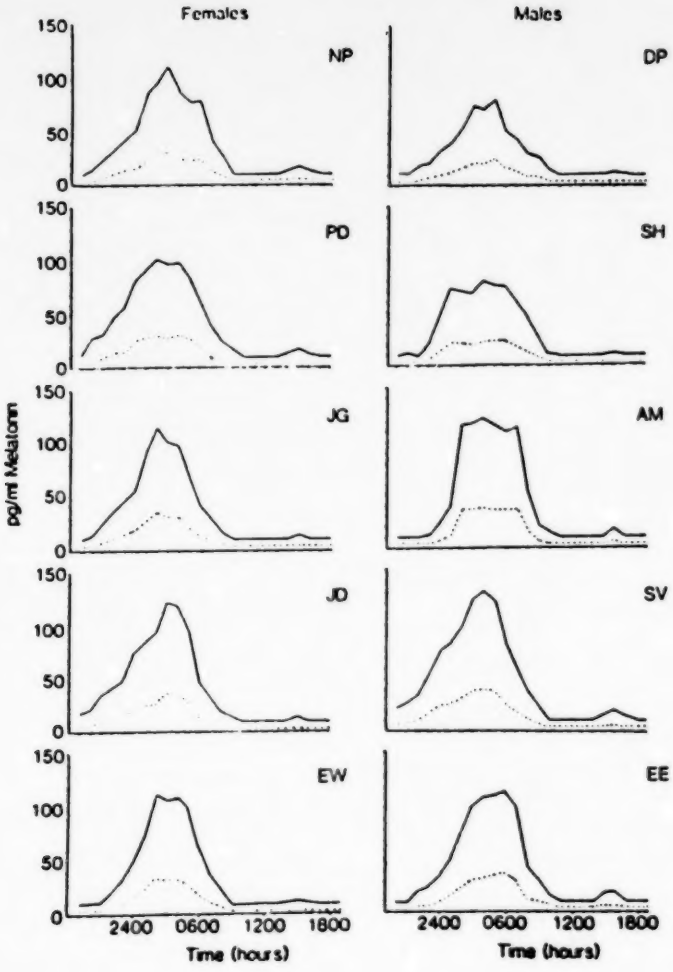

FIGURE 3: THE 24 HOUR PROFILES OF PLASMA AND SALIVARY MELATONIN SECRETION IN HEALTHY VOLUNTEER SUBJECTS (10)

The synthesis and secretion of melatonin is regulated primarily by external environmental signals and internal hormonal feedbacks. Light cues acting via the retinopineal tract (18) are among the most important modulators. The seasonal change in human melatonin levels correlates closely with natural daylength, implicating that the cycle shift is related to photoperiod (12). In constant darkness, the melatonin rhythm persists and maintains its 24 hour cycle (14, 20). The rhythm is therefore endogenous, light serves to signal the timing and amplitude of these natural rhythms. Studies of humans exposed to darkness or sleep during the day showed no change in their melatonin levels (15). Thus, light functions in the "setting" of an endogenous circadian "clock" (16). Light does, however, have a clearly demonstrated inhibitory effect on melatonin secretion (10, 14). Studies of human responses to light exposure revealed that light of sufficient intensity (500 - 2500 lux) causes an acute suppression of night time melatonin (12, 14). Exposure to very bright light (>2500 lux) can effectively advance or delay melatonin patterns (12, 17). It was concluded that

only such extremely bright light could produce this suppression in humans but recent results demonstrate that most individuals show a small response to less bright (300 lux) light (11). Nevertheless, this intensity is still greater than normal indoor lighting. Other mammals, including laboratory animals, respond readily to light of lower intensities (14).

The precise function of the pineal gland and melatonin in humans is not completely understood. A potential role for melatonin is in the timing and induction of sleep (10, 11, 16). Altered melatonin rhythms have been found in association with insomnia, jet lag, shift work and other sleep disturbances (11, 12). Melatonin has been implicated in a variety of psychiatric disorders including depression, schizophrenia and seasonal affective disorder (12, 13, 19) and also in neurological disorders such as Parkinsonism, Huntingtons chorea and epilepsy (13, 17). It has been proposed that melatonin also plays a part in the regulation of the onset of puberty (15). In animals, it has been demonstrated that melatonin can inhibit gonadal development (16, 18). There are however, also reports of progonadal effects (16). Additionally, the results of studies measuring melatonin levels in children and adolescents have been conflicting (17). It is plausible that melatonin may contribute to the control of reproductive functions and sexual maturation in animals, but no such role can be clearly defined in humans (18, 21).

Melatonin appears to be closely linked to the endocrine system, and shows disturbed rhythms in various endocrinological disorders (10,15). It is postulated that melatonin may modulate several endocrine systems including pituitary gland hormones, products of the adrenal cortex and medulla, thyroid hormones, reproductive hormones and possibly calcium regulatory hormones and insulin (15). Although melatonin may be altered in various pathological conditions, it can be argued that many of these are observations of changes secondary to the underlying disease and have no causal connection (11). It is generally agreed that the main function of the pineal is the transduction of light and dark information in relation to biological rhythms (11).

Recent hypotheses have linked melatonin and the immune system, proposing that "the pineal gland acts physiologically as a buffer device by quenching the adverse immunologic effects of stress through circadian release of melatonin, acting, in part, via an immunostimulating opiatergic mechanism" (27). This is evidenced by reports that inhibition of melatonin synthesis results in depressed humoral and cellular immune responses in mice (23, 25). Inhibition is achieved functionally by exposure to constant light and pharmacologically by the administration of beta blockers. The immune impairment, evidenced by significantly reduced antibody production and atrophy of thymolymphatic tissue, can be reversed by melatonin administration (24, 25). Further studies showed that melatonin treatment during primary immunization in mice also enhanced cellular and humoral immune responses. It was also demonstrated that melatonin counteracts the immunosuppressive effects of acute anxiety stress or corticosterone induced stress in mice (24, 25).

The opiod receptor blocker, naltrexone, inhibits the immunostimulatory effect of melatonin in mice. In contrast, naltrexone showed no effect when given alone (27). This suggests that melatonin interacts somehow with opiate peptides (23, 29). Thus it is hypothesized that the ability of melatonin to stimulate the

immune system may not be exerted directly on immunocompetent cells but mediated via the endogenous opiod system (24). Whatever the precise mechanism, the evidence that melatonin can have immunomodulating effects suggests that it may also contribute to the immunoregulation of malignancy (29).

Growing experimental evidence suggests that the pineal gland and melatonin play a role in neoplastic disease (7). This is based on the results of numerous investigations, ranging from the measurement of melatonin levels in human cancer patients to melatonin administration and pineal gland removal in laboratory animals. Both in vivo and in vitro studies have revealed a significant relationship between melatonin, the pineal gland and cancer (7).

Early evidence for the pineal and cancer association came from the post mortem examinations of the pineal glands of patients with malignant disease. Changes in pineal weight, histology and biochemistry were observed (8,34). These findings, however, were not consistent, as other researchers found no significant changes in the pineal glands of cancer patients (8, 32). In animal studies there are reports of morphological change in the pineal glands of tumor bearing animals versus normal animals (30). Whether such changes are evidence of a relationship between the pineal and malignancy is unclear. However, these observations provided the basis for further investigations.

Several studies have focused on the measurement of serum and urinary melatonin levels in oncological patients, with contradictory results. Both elevated and depressed melatonin levels and altered circadian melatonin rhythms were found in different groups of cancer patients as compared to healthy controls or patients with non-malignant disease (8, 10, 34, 35). Hormone dependent tumors such as breast and prostate cancer have been of particular interest and decreased night-time melatonin was found in groups of these patients (33). It is not known whether these changes precede the tumor and contribute to its growth or whether they are a consequence of a reaction against the neoplasm (8, 34). The changes could also be secondary to the metabolic and endocrinological responses to the disease (35). The presence of a malignancy constitutes a stress to the body, and stress is known to influence melatonin secretion (34, 37). Stress and disease also initiate adaptations in the immune system. Since a link between melatonin and the immune system appears to be likely, melatonin levels could be affected by an altered immune state (34). Although the mechanisms are unknown, the results of these studies support the conclusion that melatonin is clearly disturbed in some cancer patients, and may contribute to the disease process.

A few additional studies investigated the results of melatonin administration to cancer patients (7, 8). Some report an improvement in these patients, but no well controlled, clinical trials have been done (8). The use of melatonin as a cancer marker and in cancer therapy is still in the experimental stage.

Melatonin may have direct antimitotic action on cells. There is some evidence that melatonin exerts an inhibitory effect on normal and neoplastic cellular proliferation (7,10,30,38). However, in vivo studies have been more successful than in vitro studies (7). This implies that the inhibition of cell proliferation may not be due to a direct action of melatonin on cellular division but is more likely mediated via other mechanisms. The discovery of cellular melatonin binding sites (15), however, supports the theory that there may be

direct interaction at the cellular level. Despite this, the evidence for a direct cellular action of melatonin remains unconvincing (7).

Much experimental work has been done using a variety of animal models involving rats, hamsters and mice. The growth of induced tumors has been studied in pinealectomized animals (animals with their pineal gland surgically removed) in comparison to animals with intact pineal glands or those that have undergone "sham" surgery. The majority of these studies found more rapid growth of transplanted and inoculated tumors in pinealectomized animals. Table 1 is a generalized list of these studies, which each used slightly different protocols. The end points used to indicate tumor progression include incidence, weight, volume and size of tumors, frequency of metastases, time latency to onset and animal survival time. Because each study looked at different features, results are listed as to whether tumor growth was stimulated, inhibited or unchanged.

TABLE 1: THE EFFECT OF PINEALECTOMY ON TUMOR GROWTH (REFS 40-75)

Studies listed by author, date, tumor system, animal and light conditions. (L = hours of light exposure, D = hours of dark exposure).

TUMOR INHIBITION	NO EFFECT	TUMOR STIMULATION
1. Stanberry et al, 1983 Melanoma Hamster (Short photoperiod 6L:18D)	1. Lapin, 1975 Polyoma virus Rats	1. Rodin, 1963 Walker carcinoma Rats
2. Kothari et al, 1984 DMBA induced mammary tumors Rats (Constant light 24L:0D)	2. Wrba et al, 1975 Polyoma virus Rats	2. Das Gupta and Terz, 1967 Melanoma Hamster
	3. Lapin, 1978 DMBA induced mammary tumors Rats	3. Das Gupta, 1968 Ovarian carcinoma Hamsters
	4. Aubert et al, 1980 DMBA induced mammary tumors Rats	4. Billiteri et al, 1969 Ehrlichs tumor Mice
	5. Tamarkin et al, 1981 DMBA induced mammary tumors Rats (high dose DMBA)	5. Barone and Das Gupta, 1970 Walker carcinoma Rats
	6. Kothari et al, 1984 DMBA induced mammary tumors Rats (10L:14D)	6. Aubert et al, 1970 DMBA induced melanoma Hamster
	7. Toma et al, 1987 Prostatic carcinoma Rats (12L:12D)	7. Barone et al, 1972 Fibrosarcoma Rats
		8. El Domeiri et al, 1973 Melanoma Hamster
		9. Lapin, 1974 Yoshida tumor Rats
		10. Guerinot et al, 1975 DMBA induced mammary tumors Rats

TABLE 1: THE EFFECT OF PINEALECTOMY ON TUMOR GROWTH (Cont'd) (REFS 40-75)

Studies listed by author, date, tumor system, animal and light conditions. (L = hours of light exposure, D = hours of dark exposure).

TUMOR INHIBITION	NO EFFECT	TUMOR STIMULATION
		11. Tamarkin et al, 1981 DMBA induced mammary tumors Rats (Low dose DMBA)
		12. Toma et al, 1987 Prostatic carcinoma Rats (12L:12D)

These results support the theory that the pineal gland has an inhibitory influence on tumors. Its removal is associated with increased proliferation and its presence in intact animals is associated with restrained growth (7).

The results of the group of studies outlined in Table 2 (another general summary) show that the administration of exogenous melatonin to pinealectomized animals reverses the stimulatory effect of pinealectomy on tumor growth. This is evidence that it is the lack of melatonin in these animals that contributes to the accelerated neoplastic growth, because replacement of the melatonin restores the growth inhibition.

TABLE 2: THE EFFECT OF MELATONIN ADMINISTRATION TO PINEALECTOMIZED ANIMALS ON TUMOR GROWTH (41,54,63,65,68,70)

Studies listed by author, date, tumor system, animal and light conditions. (L = hours of light exposure, D = hours of dark exposure).

TUMOR INHIBITION	NO EFFECT	TUMOR STIMULATION
1. El Domieri et al, 1973 Melanoma Hamsters	1. Aubert, et al, 1980 DMBA induced mammary tumors Rats (Constant light, 24L:0D)	
2. Lapin and Ebels, 1976 Yoshida tumor Rats	2. Tamarkin et al, 1981 DMBA induced mammary tumors Rats	
3. Aubert et al, 1980 DMBA induced mammary tumors Rats (Diurnal light 12L:12D)		
4. Lapin and Frohwein, 1981 Yoshida tumor Rats		
5. Shah et al, 1984 DMBA induced mammary tumors Rats (24L:0D and 10L:14D)		

Animals exposed to light 24 hours a day are "functionally" pinealectomized. Their pineal glands remain intact but secretions are inhibited by the constant

light (20). Several experiments have shown that tumor growth in these animals is usually increased as compared to animals housed in normal lighting conditions. Table 3 summarizes these results. Again, the lack of pineal secretions is associated with augmented tumor growth.

TABLE 3: THE EFFECT OF CONSTANT LIGHT ON TUMOR GROWTH (41,56,59,60,68,72)

Studies listed by author, date, tumor system, and animal.

TUMOR INHIBITION	NO EFFECT	TUMOR STIMULATION
	1. Aubert et al, 1980 DMBA induced mammary tumors Rats	1. Hamilton, 1969 DMBA induced mammary tumors Rats
		2. Tessman et al, 1972 Walker carcinoma Rats
		3. Kothari et al, 1982 DMBA induced mammary tumors Rats
		4. Kothari et al, 1984 DMBA induced mammary tumors Rats
		5. Shah et al, 1984 DMBA induced mammary tumors Rats

Researchers have also investigated the effects of exogenous melatonin administration on the development of induced tumors in intact animals. These results are listed in Table 4. It is important to note that the methodologies vary widely from one study to another. Comparisons are further confounded by differences in melatonin dosage, route, time of administration and lighting schedules. For example, melatonin given in the morning tends to promote tumor development, whereas evening melatonin tends to slow tumor growth (42, 45, 47, 66, 69, 70). Short and long photoperiods have varying effects on different tumor types (45). The majority of studies show tumor growth is inhibited by melatonin, however a significant number show stimulated tumor growth or no effect at all (Table 4). Although these result are not definitive, they lend support to an anti-neoplastic role for melatonin. They do show that any effects can be influenced by other factors, particularly photoperiod (7).

TABLE 4: THE EFFECT OF MELATONIN ADMINISTRATION ON TUMOR GROWTH (REFS 40-75)

Studies listed by author, date, tumor system, animal, time of melatonin administration and light conditions.
(MEL = melatonin, L = hours of light exposure, D = hours of dark exposure).

TUMOR INHIBITION	NO EFFECT	TUMOR STIMULATION
1. Anisimov et al, 1973 Transplanted mammary tumor Mice	1. Bostelmann et al, 1971 Walker carcinoma Rats	1. Hamilton, 1969 DMBA induced mammary tumors Rats (diurnal light 12L:12D)

TABLE 4: THE EFFECT OF MELATONIN ADMINISTRATION ON TUMOR GROWTH (Cont'd)
(REFS 40-75)

Studies listed by author, date, tumor system, animal, time of melatonin administration and light conditions.
(MEL = melatonin, L = hours of light exposure, D = hours of dark exposure).

TUMOR INHIBITION	NO EFFECT	TUMOR STIMULATION
2. Buswell, 1975 Leukemia Mice	2. Huxley and Tapp, 1972 Yoshida tumor Mice	2. Lapin and Ebels, 1976 Lewis Lung carcinoma Mice
3. Lapin and Ebels, 1976 Fibrosarcoma Mice	3. Ghosh et al, 1973 Melanoma Hamsters	3. Bartsch and Bartsch, 1981 Ehrlichs tumor Mice (MEL am, 13L:11D)
4. Karmali et al, 1978 Transplanted mammary tumor Rats	4. El Domieri et al, 1973 Melanoma Hamsters	4. Bartsch and Bartsch, 1981 Fibrosarcoma Mice (MEL am, 13L:11D and 8L:16D)
5. Aubert et al, 1980 DMBA induced mammary tumor Rats (MEL pm, 12L:12D)	5. Lapin and Ebels, 1976 Yoshida tumor Rats	5. Stanberry et al, 1983 Melanoma Hamsters (MEL am, pm and continuous, 14L:10D)
6. Aubert et al, 1980 Established mammary tumors Rats	6. Aubert et al, 1980 DMBA induced mammary tumors Rats (constant light 24L:0D, MEL pm)	6. Buzzell, 1988 Prostate carcinoma Rats (MEL pm, 12L:12D)
7. Tamarkin et al, 1981 DMBA induced mammary tumors Rats (MEL pm)	7. Lapin and Frohwein, 1981 Yoshida tumor Rats (MEL pm)	
8. Lapin and Frohwein, 1981 Yoshida tumor Rats (MEL am)	8. Bartsch and Bartsch, 1981 Ehrlichs tumor Mice (MEL midafternoon)	
9. Bartsch and Bartsch, 1981 Ehrlichs tumor Mice (MEL pm, 13L:11D and 8L:16D)	9. Stanberry et al, 1983 Melanoma Hamsters (MEL previous to tumor, 14L:10D)	
10. Bartsch and Bartsch, 1981 Ehrlichs tumor Mice (MEL am, 8L:16D)	10. Toma et al, 1987 Prostatic carcinoma Rats (12L:12D, MEL pm)	
11. Bartsch and Bartsch, 1981 Fibrosarcoma Mice (MEL pm, 13L:11D and 12L:12D)	11. Buzzell et al, 1988 Prostatic carcinoma Rats (MEL pm and continuous, 12L:12D)	
12. Stanberry et al, 1983 Melanoma Hamster (MEL previous to tumor, 6L:18D)		
13. Shah et al, 1984 DMBA induced mammary tumors Rats (Constant light 24L:0D, MEL pm)		
14. Blask et al, 1986 DMBA induced mammary tumors Rats (MEL pm)		
15. Wrba et al, 1986 Mammary tumors Mice		
16. Toma et al, 1987 Prostatic carcinoma Rats (12L:12D, MEL pm)		
17. Philo et al, 1988 Prostatic carcinoma Rats (MEL pm)		

It has been demonstrated that exposure to electric and magnetic fields can alter the pattern of melatonin secretion in experimental animals. Night time release of melatonin was suppressed in rats exposed to extremely low frequency electric fields (77, 78). Additional laboratories have confirmed these results (79). Rats exposed to magnetic fields only also showed an inhibition of the night time melatonin peak (80). This melatonin suppression seems to be an all-or-none response to the fields and when exposure is stopped normal melatonin rhythms are restored (9).

Several mechanisms for these effects have been proposed. These mechanisms are hypothesized on the assumption that the field changes are sensed by the nervous system and that the responses are neuronally rather than humorally mediated (9). The fields may be sensed by a subconscious retinal detection or by other sensory stimulatory pathways. They may be causing changes at the cellular level, perhaps by influencing ion flow across cellular membranes and charge distribution. Nerve function may be directly altered by a field induced ion cyclotron effect or the fields may be coupling to the nerve bundles themselves (9). Currently the direct coupling and ion efflux models are the most popular (9), however more work is needed to allow any reliable conclusions to be made.

That melatonin likely plays a role in neoplastic development has been established (76), although the complete mechanisms are unknown. If exposure to electric and magnetic fields can alter melatonin levels, it is hypothesized that electromagnetic fields could indirectly influence cancer progression by their effects on the pineal gland and melatonin. The role of melatonin has been specifically implicated in the development of breast cancer (7,51,58,71). The pineal gland has a modulatory influence on the neuroendocrine system, and alterations in melatonin can give rise to shifts in estrogen and prolactin levels (9). These hormones are important in the etiology of breast cancer (82). There is disagreement over whether it is increased or decreased pineal function that raises the risk of breast cancer (51, 71). It is breast cancer and other hormone promoted cancers such as prostate which are thought to be particularly sensitive to the electromagnetic field induced changes in melatonin (9, 82). The relationship between melatonin and the immune system (27) may lead to a future link to leukemia (9). These concepts provide a foundation for the development of testable hypothesis to determine the extent of the association, if any, between electromagnetic fields, the pineal gland and cancer.

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